- co-culturing of the blood mononuclear cells and progenitors, after washing of platelets, granulocytes and erythrocytes, for 4 to 10 days, in a medium allowing differentiation of monocytes into macrophages and myeloid progenitors into polynuclear cells.

R E M A R K S

It is believed that this application has been amended in a manner that places it in condition for allowance at the time of the next Official Action.

In the outstanding Official Action, Applicants note with appreciation that Groups I and II have been re-joined. However, Applicants again respectfully traverse the restriction of Groups III - VII.

SROUR et al. 5,672,346 disclose human pluripotent hematopoietic stem cell enriched compositions. The compositions comprise substantially homogeneous populations of human hematopoietic cells characterized as CD 34^{+}, HLA-DR^{1}, and c-kit receptor positive. They are capable of in vitro self-renewal and differentiation to cells of erythroid, myeloid, and megakaryocytic lineage. The cells are also capable of expansion of cell numbers (See col. 4, line 58).

SROUR et al. also disclose a method of obtaining persistent maintenance of grafted human hematopoietic cells in a

mammal, which includes grafting a mammal *in uetero* with such cellular composition. By grafting human hematopoietic cells in a mammal, peripheral blood cell compositions containing, among others, CD14+ monocytes, may be obtained, but they do not contain macrophages. Moreover, if they were to contain macrophages, it would be obvious to one skilled in the art that the percentage would be much lower than 10%.

Moreover, Applicants submit that the cell compositions disclosed by SROUR et al. do not present any anti-infectious properties, as do the compositions of the present invention. Thus, it is respectfully submitted that the outstanding Official Action fails to show the special technical feature of the present invention.

It is believed that this application has been amended in a manner that places it in condition for allowance at the time of the next Official Action.

Claims 1-19 have been canceled and new claims 20-33 have been added. Support for new claims 20-33 may be found in previously pending claims 1-19 and generally throughout the specification. The Examiner's attention is respectfully directed to claim 20. Claim 20 recites a cell composition comprising macrophages. The macrophages are present in the amount of about 10 to about 70%. Support for this recitation may be found at page 2, line 20 of the present specification.

In the outstanding Official Action, a new title was required that was indicative of the invention to which the claims are directed. In the present amendment, the title of the invention has been amended to recite "Cell Compositions Containing Macrophages, Presenting Anti-Infectious and Hematopoietic Properties". Thus, it is believed that the new title clearly indicates the subject matter of the claimed invention.

In the outstanding Official Action, the drawings were objected to because of errors listed on the PTO-948 form. Upon reviewing the PTO-948 form, it is believed that the objections to the drawings are due to the photocopy quality of the present figures. Applicants are currently in the process of attending to the corrections of the drawings in the present application. Upon receiving the corrected drawings, Applicants will promptly file the new drawings.

In the outstanding Official Action, claims 6, 13-15 and 18-19 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

It is believed to be apparent that claims 20-33 have been drafted in a manner so as to obviate the indefiniteness rejections of the outstanding Official Action. While claims 6

and 13 have been canceled, claims 14 and 18 have been amended to recite "a composition". Moreover, claims 14 and 18 were amended to delete the phrase "pharmaceutical composition". As thoughtfully suggested by the Examiner, claims 14 and 18 have been amended to recite that the composition contains a pharmaceutically acceptable carrier and as an active agent, the composition according to claim 20. Claims 15-19 have been amended to insert the word "and" on the penultimate line of each claim. Thus, it is believed to be apparent that claims 20-33 are definite to one of ordinary skill in the art.

Claims 1, 3 and 14 were rejected under 35 USC §102(b) as allegedly being anticipated by YAMAMOTO 5,326,749. This rejection is respectfully traversed.

YAMAMOTO relates to a macrophage activating factor prepared in vitro by treating glycosylated vitamin-D binding protein with glycosidases. Vitamin D binding protein (DBP) is a polypeptide having attached thereto a specific oligosaccharide and is a precursor of the macrophage activating factor. DBP is converted to the macrophage activating factor by the action of glycosidases of B and T cells that remove portions of the oligosaccharide. A macrophage activating factor according to the invention could be useful as an adjuvant for vaccination to enhance and accelerate the immune response (See column 7, lines 50-55).

YAMAMOTO cites the enhancement of phagocytic properties of macrophages upon incubation of peritoneal cells with lysophospholipids or alkylglycerols. YAMAMOTO states at column 3, lines 64-68 that the administration of the macrophage activating factor enhances phagocytic macrophage activity, and therefore could be used as a therapeutic agent for infectious diseases. At column 7, lines 10-15, YAMAMOTO defines the activation of macrophages as enhanced phagocytic activity, which may lead to enhanced processing and presentation of antigens by the macrophages, and implicitly to their enhanced capacities in immune responses. Examples disclosed by YAMAMOTO also describe the testing of macrophages subsequently to the action of the macrophage activation factor, such testing is restricted to a phagocytic assay.

Applicants believe that YAMATO fails to describe or suggest a cellular composition that exhibits hematopoietic activity, or contains macrophages as set forth in the present application. Moreover, Applicants note that while the mixture of "peritoneal cells" disclosed by YAMAMOTO contains macrophages, B lymphocytes and T lymphocytes, such a mixture does not contain myeloid nor progenitor cells.

Thus, it is believed that YAMAMOTO anticipate or render obvious the claimed invention. It is respectfully submitted that YAMAMOTO fails to disclose or suggest the claimed invention.

In view of the present amendment and the foregoing remarks, therefore, it is believed that this application is now in condition for allowance, with claims 20-33, as presented. Allowance and passage to issue on that basis is accordingly respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

YOUNG & THOMPSON

By Philip A DuBois

Philip A. DuBois
Agent for Applicants
Registration No. 50,696
745 South 23rd Street
Arlington, VA 22202
Telephone: 703/521-2297

December 2, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The **TITLE** has been changed, declaration excepted, to the following:

[CELL COMPOSITION CONTAINING MACROPHAGES, PRESENTING ANTI-INFECTIOUS AND HEMATOPOIETIC PROPERTIES, AND A PROCESS FOR PREPARING THE SAME]

--CELL COMPOSITIONS CONTAINING MACROPHAGES, PRESENTING ANTI-INFECTIOUS AND HEMATOPOIETIC PROPERTIES--.

Page 1, the paragraph beginning on line 16 has been replaced as follows:

--However, it offers several drawbacks including cost (the process of selection of cells on antibody coated beads), limited amounts of progenitor cells recovered, and delays in immune reconstitution (resulting in infectious complications in the post transplant period).--

Page 2, the paragraph beginning on line 15 has been replaced as follows:

--The aims of the invention are achieved by a cell composition containing macrophages, [myeloïd] myeloid cells and progenitor cells, with said progenitor cells being preferably present in a mean ratio of at least about 1%, preferably about [0,1] 0.1 to 20%, with said [myeloïd] myeloid cells being preferably present in an amount of about 10% to about 30%, with

said macrophages being preferably in an amount of about 10 to about 70%, these percentages being expressed with respect to the total number of cells.--

Page 2, the paragraph beginning on line 22 has been replaced as follows:

--Macrophages, [myeloïd] myeloid cells and progenitor cells are defined as $CD14^+$ and $CD64^+$ cells (macrophages), $CD33^+$ cells (myeloid cells) and $CD34^+$ cells and/or GM-CFU (progenitor cells). GM-CFU are cells able to form colonies of granulocyte and macrophage in cytokine containing semi-solid culture medium after 14 days of culture.--

Page 3, the paragraph beginning on line 5 has been replaced as follows:

--According to an advantageous embodiment of the invention, the progenitor cells contain from about [0,1%] 0.1 to about 20% of stem cells, expressed with respect to the total number of progenitor cells.--

Page 3, the paragraph beginning on line 10 has been replaced as follows:

--According to an advantageous embodiment, the progenitor cells are generated from and possibly included in peripheral blood mononuclear cells, and in particular are chosen among:

[myelo-erythroïd] myelo-erythroid progenitor cells, [myeloïd] myeloid progenitor cells, [lymphoïd] lymphoid progenitor cells or a mixture thereof.--

Page 3, the paragraph beginning on line 20 has been replaced as follows:

--In the cell composition of the invention, the macrophages, [myeloïd] myeloid cells and the lymphocytes if present, are included in/or generated from blood mononuclear cells.--

Page 4, the paragraph beginning on line 3 has been replaced as follows:

--4) facilitating engraftment by the enhanced amount of stem cells, of hematopoietic cells, progenitors of [myeloïd] myeloid cells, erythroid and lymphoid as well as of cells at intermediate states of differentiation present in the graft,--

Page 4, the paragraph beginning on line 9 has been replaced as follows:

--The invention also relates to a process for the preparation of a cell composition containing macrophages, [myeloïd] myeloid cells and progenitor cells, with said progenitor cells being preferably present in an amount of about [0,1 %] 0.1% to about 10%, with said macrophages being preferably in an amount of about 10 to about 60%, these percentages being expressed with respect to the total number of cells, comprising

the step of mobilization of the progenitor cells in the blood of a patient, for instance by premedication of said patient with G-CSF and/or GM-CSF, or G-CSF and cyclophophosphamide, thus increasing the amount of progenitor cells in peripheral blood.--

Page 4, the paragraph beginning on line 21 has been replaced as follows:

--The process of the invention can comprise an additional step of coculture of the blood mononuclear cells and progenitors, after washing off the platelets, the granulocytes and erythrocytes, for about 4 to about 10 days, in a medium allowing differentiation of monocytes into macrophages and [myeloïd] myeloid progenitors into polynuclear cells.--

Page 5,the paragraph beginning on line 8 has been replaced as follows:

--It is to be noted that cellular product obtained after *ex vivo* differentiation and expansion contains stem cells, progenitor cells, [myeloïd] myeloid cells, T lymphocytes and differentiated macrophages which are activated (for example by γ interferon) at the end of the process. The coculture for 3 to 12 days performed at 37°C in non adherent bags and defined medium (IMDM basis) allows increased recovery of $CD34^+$ cells and/or of intermediate hematopoietic progenitor cells. This means that normal hematopoietic progenitors are not only spared by activated

macrophages, but are also stimulated to greater proliferation and differentiation.--